

DOCKET NO. VIP-4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kurt Hertogs et al.

Serial No.: 09/580,491

Art Unit: 1631

Filed : May 30, 2000

Examiner: Galitsky, Nikolai M.

For : NEW MUTATIONAL PROFILES IN HIV-1 PROTEASE AND REVERSE TRANSCRIPTASE CORRELATED WITH PHENOTYPIC DRUG RESISTANCE

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Todd F. Volyn
Name of applicant, assignee, or Registered Representative

TECH CENTER 1600/2900

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AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached is an Appeal Brief for the above-captioned patent application.

Please charge Deposit Account No. 10-0750/VIP-4/TFV in the name of Johnson & Johnson in the amount of \$320.00, representing the cost of filing a Brief on Appeal in the above-captioned matter.

The Commissioner is hereby authorized to charge any additional fees which may be required to Account No. 10-0750/VIP-4/TFV. This Authorization is being submitted in triplicate.

Respectfully submitted,

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DATED: October 29, 2002



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Commissioner For Patents
Washington, D.C. 20231

APPEAL BRIEF

Dear Sir:

Real Party in Interest

Johnson & Johnson, a New Jersey corporation, is the real party in interest subject to an
obligation of assignment on the part of the inventors.

Related Appeals and Interferences

None.

Status of Claims

Pending claim 7 of the instant application has been finally rejected on April 29, 2002. Claims 1-6 and 8-30 of the application were the subject of restriction and election of species requirements. These claims are not at issue in this appeal.

Status of Amendments

No amendments have been filed subsequent to the issuance of the final rejection of April 29, 2002.

Summary of the Invention

The invention is a method for evaluating the effectiveness of an antiviral therapy of an HIV infected patient. In the method, a patient sample is collected from which it is determined whether the patient has nucleic acid(s) comprising one or more mutations. The mutations are single mutations or combinations of mutations (set forth in the claim) with some mutations indicative of resistance to Non-Nucleoside Reverse Transcriptase Inhibitor(s) (NNRTI), other mutations indicative of resistance to Nucleoside Reverse Transcriptase Inhibitor(s) (NRTI), and yet others indicative of resistance to Protease Inhibitor(s) (PI). The presence of a mutation referred to as 88T has particular relevance to this appeal. The claim at issue recites that the 88T mutation correlates to PI resistance. That is, the presence of the 88T mutation found in a patient sample indicates PI resistance.

Issues

1. Whether claim 7 is obvious over a reference to Condra et. al., in view of WO 99/67427 to Petropoulos? The Condra reference is a journal article from the *Journal of Virology*, Dec. 1996 entitled, *Genetic Correlates of In Vivo Viral Resistance to Indinavir, a Human Immunodeficiency Virus Type 1 Protease Inhibitor*.

2. Whether the application is objectionable according to 35 USC § 112 for inclusion of an Internet address and a single description of three graphical comparisons illustrative of the results of a single example?

Grouping of Claims

There is only one claim at issue in this Appeal.

Argument

1. Claim 7 is not obvious over the cited references.

The Examiner maintains that the inclusion of mutation N88T in a “generic listing of mutation resistance” in Table 1 of the Condra reference renders the instant invention obvious. Line 9 of Office Action of 4 March, 2002. The Examiner argues that the presence of this mutation among a number of other mutations found in a single patient and correlated with phenotypic data showing drug resistance establishes a discovery from which the instant invention is a mere obvious modification. The role of the Petropoulos reference in this rejection is not clear but is considered below anyway.

a. **The references are not properly combinable.** The Petropoulos reference, particularly the portion cited by the Examiner in the Rejection of 17 September, 2001 (page 73, lines 4-5), is directed entirely to resistance to Nucleoside Reverse Transcriptase Inhibitors (NRTI). *See also*, Petropoulos at Page 1, line 30. The Condra reference is directed entirely to resistance to Protease Inhibitors (PI) and more particularly, a single PI, Indinavir.

A fair reading of both cited references reveal that if a correlation exists between PI and NRTI resistance, it is as yet undeterminable. Indeed, even within a single class of therapeutics Condra found that “three [other] viral isolates evaluated in the same study exhibited such divergent patterns of substitutions in the protease that a simple basis for the resistance could not be defined.” Condra at page 1, column 2; *See also*, page 8273, bottom of column 2 (cross reactivity even among PI’s is not amenable to pattern analysis). Neither reference contains a single statement that can relate one to the other nor is there any basis for making such an inference. Neither has the Examiner offered any insight into any reason or indication of the rationale for combining these references. Without one, the references are not properly

combinable and the rejection must stand or fall on the strength of each reference individually. *In re Rouffet*, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998).

b. The claimed invention is not obvious over the cited references individually. In the instant invention, the 88T mutation is correlated with resistance to PIs. The Petropoulus reference, on the other hand, is directed to NRTIs. Accordingly, even if Petropoulus identifies mutations that correlate with drug resistance with perfect clarity, it would be inapposite to the finding that 88T correlates with resistance to PI since resistance to NRTIs tells one nothing at all of PI resistance. In fact, Petropoulus does not even mention the 88T mutation. Thus, there is no basis for using Petropoulus by itself to render the instant invention obvious as there is no conceivable way to modify anything described by Petropoulus to obtain the instant invention and there is no reason proffered for doing so. *In re Heck*, 216 U.S.P.Q. 1038 (Fed. Cir. 1983).

As noted above, the Condra reference is directed to a study of PI resistance. Table 1 of the reference provides a comprehensive summary of protease mutations found in viral isolates taken from 21 different patients. One patient, patient "O", displayed PI resistance when the combination of eight different mutations was present. The 88T mutation of the instant invention was one of the mutations present in this combination. This is the only place in the entire reference in which 88T appears. The Examiner arrives at the conclusion that this table entry is enough to indicate that "the presence of N88T in any combination of mutants as responsible for resistance." Office Action of 4 March 2002, page 3, line 15.

In fact, the Condra reference teaches something much different. Table 1 shows 29 different combinations of mutations in isolates that display PI resistance. Of these, 17 different combinations of mutations are found in isolates with an IDV CIC₉₅ greater than or equal to 1500 nM. There are 12 different combinations of mutations found in isolates with an IDV CIC₉₅ greater than or equal to 3,000 nM. There is only one isolate in which N88T appears and that occurs within a combination of eight different mutations.

Which of the mutations does one select as a marker for PI resistance? Assuming that one skilled in the art started with a list of the 12 different combinations of mutations correlating with the IDV CIC₉₅ greater than or equal to 3,000 nM, the chances of selecting the N88T mutation as a marker whose presence correlates with PI resistance is astronomical since one cannot be sure whether all mutations within a listed combination are necessary or sufficient to make such a correlation, whether only a subset of such mutations are necessary or sufficient, whether an individual mutation is necessary or sufficient (including whether 88T alone correlates with PI

resistance), and which combination or which individual mutation from within the recited combination is necessary or sufficient to make such a correlation.

Even if one somehow concluded that they should consider a marker for PI resistance from the findings of patient O, the chance of identifying N88T as a marker of interest is very small since one must consider all combinations of the eight mutations as well as each one individually. Even Condra, in reviewing combinations more indicative of resistance than the one containing N88T, noted “no invariant combination clearly coincided with the loss of inhibition susceptibility”. *Condra* at Col. 2, Line 18, pp. 8271. At best then, Condra provides the basis for an “obvious to try” argument where there is far from anything like a reasonable likelihood of success. Of course, such an argument fails to provide the basis for an obviousness rejection. *In re O’Farrell*, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

Even given a reading most closely aligned with the Examiner’s position, Condra actually teaches away from the use of N88T as a PI resistance marker. First, the Examiner notes that Condra, in his abstract, states that

“No single substitution was present in all resistant isolates, indicating that resistance evolves through multiple genetic pathways. Despite this complexity, all of 29 resistant isolates tested exhibited alteration of residues..., suggesting that screening of these residues may be useful in predicting the emergence of resistance. We also extended our previous finding that IDV-resistant viral variants exhibit various patterns of cross-resistance to a diverse panel of HIV-1 protease inhibitors. Finally, we noted an association between the number of protease amino acid substitutions and observed level of IDV resistance.”

In citing this passage, the Examiner left out an important aspect of the report. The phrase, “M-46 (to I or L) and/or V-82 (to A, F, or T)” is the phrase replaced by the Examiner’s ellipsis. When inserted back into the passage, it shows the heavy emphasis the investigators put on a discrete set of mutations that did not include N88T.

This emphasis is seen again in the second paragraph of column 2 of 8271, “An examination of the protease sequences in the viral isolates over time (Table 1) showed a high frequency of substitutions at several amino acid residues, especially... M-46(to I or L) ...V-82 (to A,F, or T)” Notably absent was any reference to N88T. Further, in the last paragraph of that same column, Condra notes, “Overall, the data demonstrated that no single pattern of amino acid substitutions in the viral protease was required for the development of resistance to

IDV...Substitutions of various combinations among at least 11 amino acid residues in the protease (L-10, K-20, L-24, M-46, I-54, L-63, I-64, A-71, V-82, I-84, and L-90) appeared to correlate with the loss of viral susceptibility to IDV as selected *in vivo*". Given the emphasis on particular mutations, the absence of any reference to N88T, and the exceedingly low probability of discerning a correlation between one member (N88T) of a combination of mutations, it can only be concluded that one skilled in the art would have been directed away from N88T when seeking a marker for PI resistance. *See e.g., In re Bell*, 26 U.S.P.Q. 2d 1529 (Fed. Cir. 1993).

For the foregoing reasons, it was error for the Examiner to reject claim 7 as obvious over Condra and Petropoulos and this rejection should be reversed.

2. Claim 7 is not vague or indefinite according to 35 USC § 112.

The Examiner continues to object to the description for a number of formalistic reasons. Each of the stated reasons are in error for which correction is sought but, in order to avoid unnecessary lengthening of prosecution, applicants are willing to make modifications upon the resolution of the action on the merits or, in the alternative, authorize Examiner's amendments.

The Examiner has objected to the inclusion of an Internet address (a URL) in the specification because the address is "executable". A URL is executable only if it is linked to a mechanism that causes a computer application such as a web browser to conduct computer operations. The software used to prepare an application dictates whether writing a URL in the text of a document will cause it to link to such an application. Many word processing programs automatically produce such a link during document drafting. In the instant case, applicants have filed an amendment in which the internet site is referenced but the URL appears only in text. Amendment, 4 March 2002. Accordingly, the application contains no executable code or hyperlinks and this basis of objection is overcome.

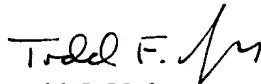
The Examiner also objects to the use of a single narrative section to describe the contents of three sub-figures that are all related and are all derived from a single example. While the presence of drawings requires a Brief Description, there is no requirement that a collection of graphical data drawn from a single example be portrayed and considered as separate figures. In the instant case, graphical data portraying IC₅₀ for three different drugs is presented. Applicants view the portrayal of this data as three sub-graphs on a single sheet as being helpful to understanding the invention which is the purpose for providing drawings at all. Thus, Applicants

see no reason to alter the specification to merely repeat the description of Figure 2 for Figure 2a, 2b, and 2c.

It is error for the Examiner to object to the description as described but applicants would authorize an Examiner's amendment to repeat the description of Figure 2 three times (once for 2a, once for 2b, and once for 2c) if necessary.

For all of the reasons cited above, the Examiner's rejection of the claims of this application were erroneous and should be reversed. Such action is respectfully solicited from the Board of Appeals.

Respectfully submitted,


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DATE: October 29, 2002

Appendix-Claims at Issue in this Appeal

7. A method of evaluating the effectiveness of an antiviral therapy of an HIV-infected patient comprising:

- (i) collecting a sample from an HIV-infected patient;
- (ii) determining whether the sample comprises at least one nucleic acid chosen from:
 - (a) a first nucleic acid encoding HIV reverse transcriptase comprising at least one mutation chosen from:
 - 1) at least one mutation chosen from 88E, 101H, 101N, 101P, 101Q, 101T, 103H, 103S, 179I, 179E, 181V, 190E, 190S, and 190T,
 - 2) mutations 103R and 179D, or
 - 3) combinations of 1) and 2),in which the presence of said at least one mutation correlates with resistance to at least one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI);
 - (b) a second nucleic acid encoding HIV reverse transcriptase comprising at least one mutation chosen from 69S, 184G, 184L, 215V, 44D, 44A, and 1181, in which the presence of said at least one mutation correlates with resistance to at least one Nucleoside Reverse Transcriptase Inhibitor (NRTI); and
 - (c) a third nucleic acid encoding HIV protease comprising at least one mutation chosen from:
 - 1) 88T
 - 2) mutations 33F and 90M, or
 - 3) combinations of 1) and 2),in which the presence of said at least one mutation correlates with resistance to at least one Protease Inhibitor (PI); and
- (iii) using the presence of said at least one nucleic acid to evaluate the effectiveness of said antiviral therapy.